Some Late Effects of Gastro-Enterostomy Performed for the Relief of Peptic Ulcer.

By R. S. Allison, W. H. Patterson, and B. M. Maxwell

from the Royal Victoria Hospital, Belfast

A writer, recently reviewing the known facts of the etiology of peptic ulcer, comments on the well-known observation that it is found in that part of the gastro-intestinal tract that is directly exposed to gastric juice, and is subjected to the greatest mechanical stress by the passage of the gastric contents.[1] Another established fact is the frequent association of ulcer with hyperchlorhydria, in from sixty to eighty-five per cent. of duodenal cases,[2] [3] and about thirty per cent. of gastric.[3] Achloryhydria is rare in either form of ulcer, and achylia gastrica believed to be unknown.[3] The importance of an excess of free HCl in the genesis of an ulcer has been illustrated by the experiments of Mann and Bollman,[4] Matthews and Dragenstedt,[5] and others. The former found that experimental jejunal ulcers were produced in about twenty per cent. of dogs after gastro-jejunostomy, when the bile and pancreatic juice had free access to the loop of jejunum used in the anastomosis. When, however, these juices were diverted and drained into the ileum and only gastric juice allowed into the loop, a jejunal ulcer developed in ninety-five per cent. of cases. Chronic gastric ulcers were also produced in dogs by the instillation of dilute HCl (0.4 per cent.) through a fistula for several hours in the day. These ulcers tended to heal if the acid was discontinued, but became chronic if it was resumed. The effects of a rich secretion of gastric juice on an empty stomach has been shown by Buechner,[6] who produced ulcers in starved rats by repeated injections of histamine. The trend of these experiments is, therefore, to assign an important rôle to the acid of the gastric juice in the formation and chronicity of ulcer, and to show that its effect can be mitigated by the neutralizing action of the alkaline duodenal juices and by the presence of food in the stomach.

The view that there is a definite ulcer diathesis seems to be gaining ground, and Hurst has spoken of the hyposthenic and hypersthenic gastric diathesis. The former, which is associated with a long hypotonic stomach, is liable to gastric ulcer, and the latter, with a short hypertonic stomach, to duodenal ulceration. The same view of a diathesis, but from a more central angle, is taken by Cushing,[7] who relates it to abnormal parasympathetic discharges and vagotonia. The motor effect on the stomach of stimulation of the vagus has, of course, been long recognized, and recently it has been demonstrated that hyperchlorhydria and ulceration may result from this procedure (Keppich,[8] Stahnke[9]). The central end of the long vagal pathway would also seem to be higher than has hitherto been supposed, for Beattie[10] has shown that stimulation of the tuber cinereum in animals causes increased gastric movements and hyperchlorhydria. If stimulation is kept up some time, hæmorrhage and ulcer formation result. These effects are abolished by section of the vagus. Moll and Flint,[11] on the other hand, have made a clinical and

experimental study of the depressive influence of the sympathetic on gastric secretion and peristalsis. It seems probable, therefore, as Cushing says, that the dual nerve supply to the stomach, the cranio-sacral autonomic system, and the thoraco-lumbar sympathetic system, represent a balanced and mutually antagonistic mechanism. "Highly-strung persons who incline to that form of nervous instability called vagotonia . . . are particularly prone to chronic hyperchlorhydria and increased gastric peristalsis, often leading to ulcer. These effects are comparable to those produced by irritative lesions made anywhere in the course of the parasympathetic . . ."

On clinical grounds also there is evidence of an ulcer diathesis in the recurrence of symptoms after careful treatment. It is possible that we have attributed such recurrences too often to indiscretions in diet, tobacco, and alcohol, when at the most these can only be accessory factors. So persistent, indeed, can the recurrence of symptoms be in some cases, that one might well apply the words of Jeremiah: "Can the Ethiopian change his skin, or the leopard his spots?"

Evidence that it may be possible to change the subject of the ulcer diathesis is forthcoming in the recent reports of cases of gastrectomy and gastro-enterostomy which have been cured of ulcer, apparently for all time, but have developed in its place an opposite type of disorder, namely, pernicious anæmia—subacute combined degeneration of the spinal cord and simple achlorhydric anæmia. It would appear that the surgical operation in these cases has been too radical, and that the picture has swung from one extreme to the other. It is noteworthy in this connection, after what has been said of the relationship between ulcer and hyperchlorhydria, that these changes have only been observed when free HCl has disappeared from the gastric juice as a result of the operation. Thus they are more prone to follow gastrectomy than partial gastrectomy, and least likely to result from gastro-enterostomy. Morley[12] found, in comparing the Polya and Shoemaker type of partial gastrectomy, that anæmia was present in twelve out of twenty-one "Polyas," and in only four out of twenty-one "Shoemakers." The explanation probably lies in the fact that the Polya type removes more of the secreting tissue and is more likely to be followed by achlorhydria.

The anæmias which follow these operations may be of two kinds. The first, pernicious anæmia, is a rare sequel. Not more than fifteen cases from the literature are mentioned by Rowlands and Simpson,[13] who contribute two cases. Some of the cases referred to—those of Moynihan[14] and Delore[15]—had insufficient evidence to support a diagnosis of pernicious anæmia, and many which gave that clinical and hæmatological picture had been operated upon for malignant disease (Hartman,[16] Hochrein,[17] Morawitz[18]). The case of Campbell and Conybeare,[19] Dennig,[20] Glanvill and Hurst,[21] and those of Rowlands and Simpson, appear, however, to be definite examples of pernicious anæmia.

The second type of anæmia is much more common, and closely resembles the simple achlorhydric or microcytic anæmia described by Faber[22] and by Witts.[23] Here there is often the same pallor of the skin and smoothness of the tongue as in pernicious anæmia; but there are additional features in the finger-nails, which have

a curious curved appearance not unlike a spoon or the shell of an oyster, and known as coilonychia. The anæmia, of course, also differs, being of the low-colour index type, and the red corpuscles are smaller in size than normal. Several of these cases following gastric operations have been described by Witts,[23] Lublin,[24] Hurst and Cosin,[25] Davies,[26] Meulengracht,[27] Vaughan,[28] and others. We have seen five cases of this type, though none of pernicious anæmia, following operation for peptic ulcer. In these subjects the former ulcer diathesis has apparently been exchanged for an anæmic diathesis with achlorhydria, and in view of their rarity and possible bearing on the etiology of peptic ulcer, a description of them is now given.

Five Cases of Simple Achlorhydric Anæmia Following Gastro-enterostomy.

Case No. 1.—*J. S., female, aged 43* :—Gastro-enterostomy for duodenal ulcer three years ago. Former notes not available. No further symptoms of indigestion. Recent nervousness, tiredness, occasional diarrhœa, flatulence. Physical examination negative, except for some pallor of the face and conjunctiva. The finger-nails have a hollow curved surface, and the tongue is smooth and clean. *Barium meal:* rapid emptying of stomach. *Fractional test meal:* achlorhydria. No occult blood in fæces. *Blood count:* red blood-cells 4,300,000, hæmoglobin 45 per cent. Van den Bergh reaction negative. Rapid improvement in blood and general condition followed large doses of iron.

Case No. 2.—*T. S., male, aged 67* :—Gastro-enterostomy for duodenal ulcer twelve years ago. Notes of former operation confirm this statement. No further symptoms until three years ago, when noticed increasing weakness, dyspnœa, sore tongue. Physical examination negative except for lemon-yellow pallor of face with malar flush. Tongue smooth atrophic type. Finger-nails normal. *Barium meal:* rapid emptying of stomach. *Fractional test meal:* achlorhydria. No occult blood in fæces. Red blood-cells 3,200,000, hæmoglobin 50 per cent., Van den Bergh negative. This case had been suspected of pernicious anæmia, and treated by liver as hepatex with little or no response. After three intramuscular injections of hepatex the maximum reticulocyte count was 1.6 per cent. The total chloride of the gastric juice as estimated after the subcutaneous injection of histamine. The fasting juice showed 35 c.c. N/10 chloride in 100 c.c. Twenty minutes after 50 c.c. of 5 per cent. alcohol it was 51 c.c. Histamine was then given, and twenty minutes later the figure was 100 c.c. N/10 chloride per 100 c.c. The case subsequently improved steadily on iron given as bipalatinoids by the mouth.

Case No. 3.—*S. W., male, aged 38* :—Long-standing recurring symptoms of pain after food relieved by food and alkali for some years, until gastro-enterostomy three years ago. A large chronic duodenal ulcer was found (confirmed). Recovery and no symptoms until a year later, when pain after food returned and there was a small hæmatemesis and melæna. At a second operation a jejunal ulcer was found (confirmed), excised, and the anastomosis undone and a gastro-duodenostomy performed. Since then there have been no symptoms, and the patient looks and feels well twenty months after the second operation. *Fractional test meal:* before the first operation showed moderate hyperchlorhydria; after the gastro-enterostomy free HCl was still present, though the curve of acidity was lower. A year later, when symptoms from the jejunum recurred, the curve of acidity showed hyperchlorhydria. Finally, after the gastro-duodenostomy achlorhydria resulted. (See fig. 1, which gives the four curves referred to.) *Blood count:* before the first and second operation the patient showed a tendency to polycythæmia. Red blood-cells 5,500,000, hæmoglobin 110 per cent. This count was actually done when he was suffering from the jejunal ulcer and after he had had the hæmatemesis. Occult blood was present in the stools at that time, but after the gastro-duodenostomy and production of achlorhydria, repeated tests of the stools for occult blood were negative. A blood-count, however, showed red blood-cells 4,500,000, hæmoglobin 50 to 60 per cent., and microcytes and poikilocytes were present in the film. Hæmoglobin rose to 85 per cent. after giving iron.

CASE No. 4.—*E. C., female, aged 42* :—Gastro-enterostomy for duodenal ulcer (confirmed) eleven years ago. No symptoms of indigestion since then. Attended hospital this year (eleven years later) complaining of rheumatic pains in the arms and shoulders. Physical examination negative. No evidence of joint or nervous disease, but looks anæmic. The tongue is smooth and glazed in appearance, and the finger-nails have a hollow curved surface. *Barium meal:* rapid emptying of stomach. *Fractional test meal:* achlorhydria. No occult blood in fæces. Hæmoglobin 50 per cent. Van den Bergh negative. Good response to iron.

CASE No. 5.—*S. H., female, aged 33* :—When aged 18 to 25 repeated attacks of pain in epigastrium one hour after food, relieved by alkali and vomiting. Notes of two periods of treatment in hospital inspected and verified. At 23 a fractional test meal showed moderate hyperchlorhydria. After 25 admitted again, symptoms worse, and barium meal showed large six-hour residue. "Tongue furred and moist." An operation was agreed upon, and a gastric ulcer was found on the lesser curvature (confirmed). This was resected and a gastro-enterostomy performed. At 31 again admitted to hospital with soreness in the upper abdomen unrelated to food and not relieved by alkali. A secondary anæmia and achlorhydria were observed. An exploratory laparotomy showed no evidence of the former ulcer, and the anastomosis was sound. The abdomen was closed. Aged 33 (this year), again under observation. On examination, no abnormal physical sign was found, except a lemon-yellow tinge round the eyes and mouth and a malar flush. The conjunctiva and mucous membranes were pale. The tongue was smooth and glazed. The finger-nails were hollow and cracked at the edges. *Barium meal:* rapid emptying of the stomach. *Fractional test meal:* achlorhydria. On an ordinary diet the fæces gave a positive benzidine reaction, but on a milk diet repeated tests were negative for occult blood. *Blood count:* red blood-cells 1,510,000, hæmoglobin 25 per cent., Van den Bergh reaction negative. Treated with thirty grains of ferri et ammon. cit., and hæmoglobin rose from 25 per cent. on 3rd July, 1933, to 85 per cent. on 7th November, 1933, with corresponding physical improvement and relief from symptoms of dyspnœa, tiredness, etc. Fig. 2 illustrates the result of fractional test meals performed in 1923 before the operation when hyperchlorhydria was present, and in 1931 and 1933 when achlorhydria was found.

These cases of simple achlorhydric anæmia following gastric operations should be distinguished from the anæmia which results from hæmorrhage from a jejunal ulcer. In the former there is no evidence of ulcer (case No. 5, aged 31, exploratory operation), or loss of blood by hæmatemesis or melæna, and certain other clinical features are present. The following table is suggested as indicating the main points of distinction.

	Jejunal Ulcer + Anæmia.	*Simple Achlorhydric Anæmia.*
Occurrence -	1—2 years after operation.	3—12 years.
Symptoms -	Pain related to food. Hæmatemesis. Melæna. Constipation.	Pain when present: indefinite. Tiredness, nervousness, dyspnœa, sore tongue, diarrhœa.
Tongue -	Rough and furred.	Smooth and atrophic.
Nails -	Normal.	Often spoon-shaped and cracked.
Gastric Analysis	Free HCl present.	Achlorhydria.
Fæces -	Occult blood +.	Occult blood negative.
Barium Meal -	Hold up in stomach. Niche.	Rapid emptying.

FIG. 1

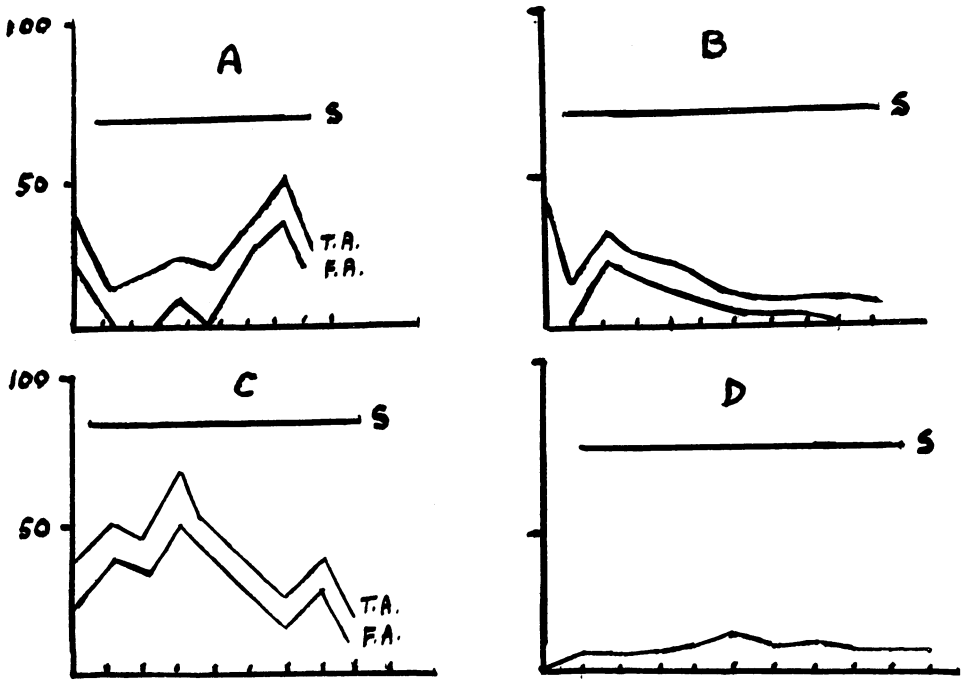
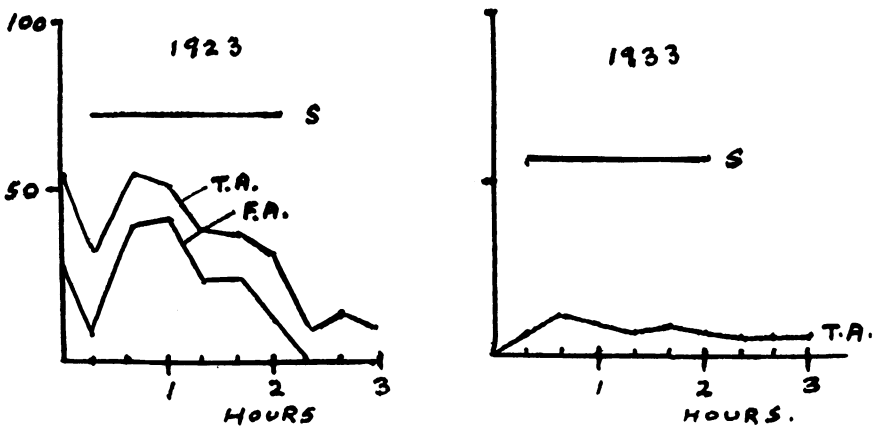


FIG. 2

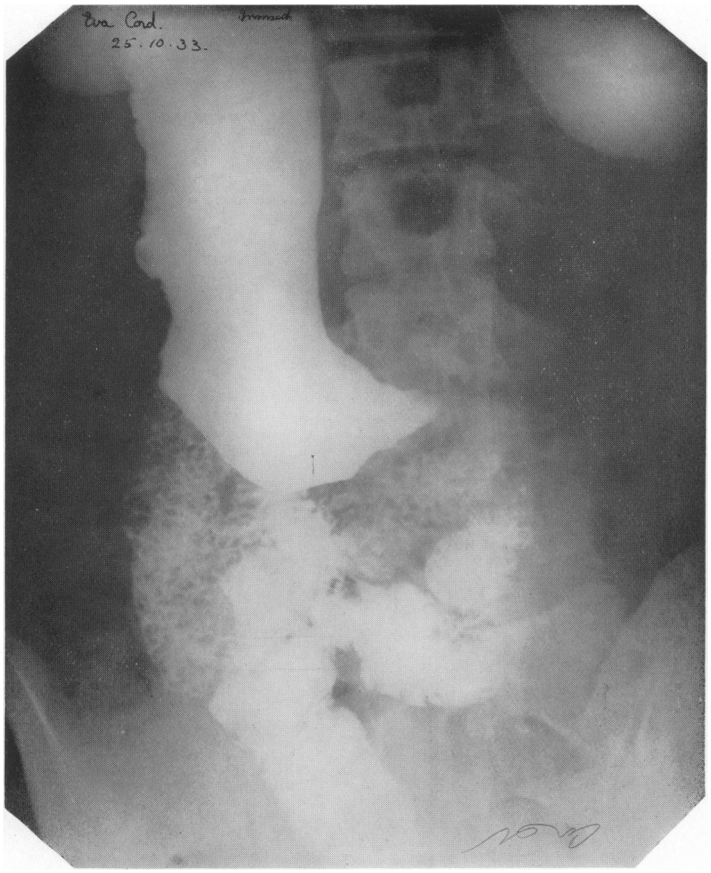


S = STARCH. T.A. = TOTAL ACIDITY. F.A. = FREE ACID.

Dr. R. S. Allison's Paper

A case of suspected jejunal ulcer after gastro-enterostomy. Radiograph taken six hours after barium meal. There is delay in emptying and a moderate residue in stomach.

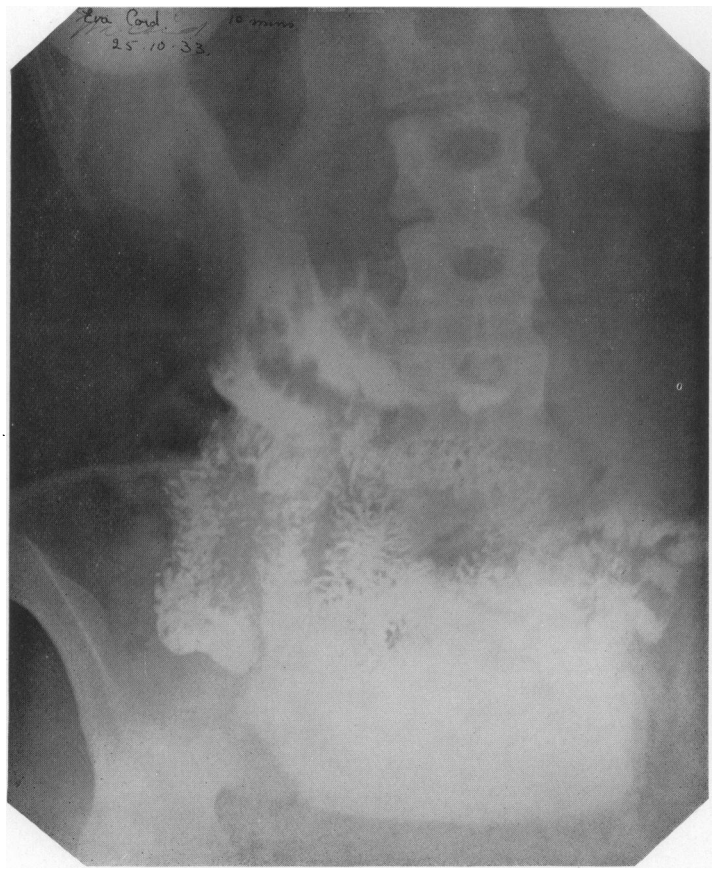
FIG. 3



CASE No. 4.

Gastro-enterostomy eleven years ago. Radiograph taken immediately after swallowing barium meal, showing stomach filled and emptying at the same time.

FIG. 4



CASE NO. 4.

Twenty minutes after fig. 3. The stomach is almost empty and the meal scattered through the small intestine.

Free HCl is usually present when jejunal ulcer recurs after operation. In Evans-Jones series of forty-two cases quoted by Hurst,[3] hyperchlorhydria was present in 70 per cent. and achlorhydria in only 4.8 per cent. In a recent investigation, Davies found in sixteen cases of jejunal ulcer, hyperchlorhydria in twelve, a normal acidity in three, hypochlorhydria in one, and none of the cases showed achlorhydria. It is possible to consider the development of achlorhydria after gastric operations in three ways: (1) When at operation the whole of the acid-bearing part of the stomach is removed, and in consequence no secretion of HCl is possible, a true achylia gastrica results. (2) When part of the acid-secreting gastric tissue is removed, and free mixture of the gastric and duodenal juice is permitted as in a partial gastrectomy. Here the achlorhydria is partly due to diminished secretion and partly due to neutralization. (3) In gastro-enterostomy, when no gastric tissue is removed, and the achlorhydria is due solely to neutralization. An alternate view would be to assume that the secretion is inhibited by the rapid exit of the food from the stomach. This undoubtedly can be demonstrated radiologically (see figs. 3 and 4), but the results of gastric analysis, when total chlorides are estimated, do not support this view. As Bolton and Goodhart[29] pointed out, the total chlorides are low in true hypochlorhydria and achylia gastrica, whereas they rise to a high level when the pseudo-hypochlorhydria or achlorhydria is due to neutralization. Case No. 2 suggests that this is what takes place in these cases. Fig. 5 also shows the curve of total chlorides in case No. 3 plotted alongside that of free and total acidity. The first analysis was made when the patient had a duodenal ulcer and before any operation was performed; the second after the final gastro-duodenostomy, which resulted in achlorhydria, yet the curves of total chloride do not differ greatly. With the achlorhydria the curve of total chloride is even greater in the later samples, and this is probably due to the presence of regurgitated bile and intestinal secretions, which, as Roberts[12] has pointed out, have a relatively high chloride concentration.

The presence or absence of occult blood in the fæces may help in deciding between these post-operative cases of achlorhydric anæmia and jejunal ulcer. We have noticed that on an ordinary diet with meat and vegetables, the former often give a positive benzidine reaction. This may be related to the finding of Deganello,[30] who investigated the fæces of a patient who had had a partial gastrectomy. Intact muscle fibre was almost constantly present. It appears likely, therefore, that the positive benzidine reaction so often obtained is due to the rapid rate of passage through the stomach and intestine. In four of the cases a negative result was obtained when they were put on a hæmoglobin-free diet.

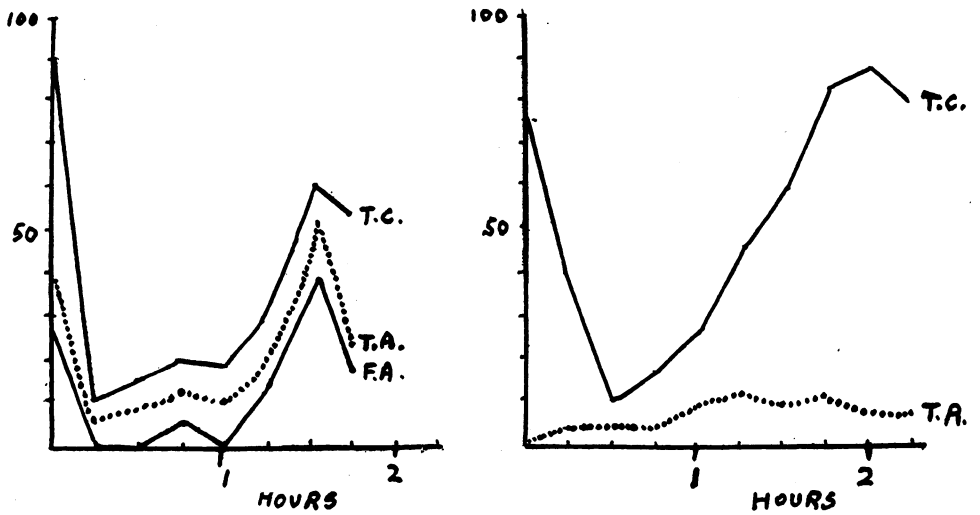


FIG. 5.

CONCLUSIONS.

In conclusion, one would again emphasize the comparative rarity of these cases after gastric operations. It is only fair to observe also that many cases of post-operative achlorhydria remain cured of their ulcer and never develop anæmia. One of us has seen a case of fifteen years' standing where the blood-count gave normal figures. The frequency of jejunal ulcer is placed at about two per cent., and certainly the occurrence of simple achlorhydric anæmia and pernicious anæmia must be rated as still less.

To return to the possibility of a change in diathesis—a swing from the hyperchlorhydria and ulcer on the one side to achlorhydria and anæmia on the other. It is clearly important to decide whether these cases are really related to the operation or not. In two of the cases (Nos. 3 and 5) there is evidence to favour a connection, but though highly suggestive it is scarcely sufficient to be conclusive. Two similar cases have been described by Hurst[25] and Vaughan.[28] If indeed it is possible that a person should at one time of his life suffer from peptic ulcer, and at another stage develop a simple idiopathic anæmia, then the way to the change is apparently to be found in the alteration from a normal or hyperacid gastric juice to a subnormal or achlorhydric juice. The increased rapidity of emptying of the stomach is also an important factor which cannot be disregarded. Such a change would lend further support to the rôle of the gastric juice, both in the formation of ulcers and in the development of anæmia. It would, by representing extremes, serve as a connecting link between ulcer on the one side, with its tendency to hyperchlorhydria, and

anæmia on the other, with its tendency to achlorhydria. In short, there may not be such a gulf between these two conditions as their respective clinical features would lead us to suppose. The connecting link which may make them part of the same chain, though at opposite ends, is the stomach and the gastric juice.

We have pleasure in acknowledging help received from the biochemical and radiological departments of the Royal Victoria Hospital, Belfast. All of the cases were seen in Medical Out-patients' except case 3, which was formerly under the care of Dr. E. I. Spriggs, to whom thanks are due for the results of the investigations before and after operation.

Bibliography.

(1) "Pathogenesis of Peptic Ulcer," *Brit. Med. Journ.*, 1933, 1, p. 279.

(2) Hunter, D., *Quart. J. Med.*, 1923, 16, p. 95.

(3) Hurst, A. F., and Stewart, M. J., "Gastric and Duodenal Ulcer," Oxford, 1929.

(4) Mann, F. C., and Bollman, J. L., *J.A.M.A.*, 1932, 99, p. 1576.

(5) Matthews, W. B., and Dragenstedt, L. R., *Surg., Gyn. and Obst.*, 1932, 55, p. 3.

(6) Buechner *et al.*, *Beitrag. z. path. Anat.*, 1928, 81, p. 391.

(7) Cushing, H., *Surg., Gyn. and Obst.*, 1932, 55, p. 1.

(8) Keppich, J., *Berl. klin. Wchnschr.*, 1921, 58, p. 414.

(9) Stahnke, E., *Arch. f. klin. Chir.*, 1924, 132, pp. 1-59.

(10) Beattie, J., *Canad. M.A.J.*, 1932, 26, p. 278.

(11) Moll, H., and Flint, E. R., *Brit. Jour. Surg.*, 1928-9, 16, p. 283.

(12) Morley, J., and Roberts, W. M., *Brit. Jour. Surg.*, 1928-9, 16, p. 239.

(13) Rowlands, R. A., and Simpson, S. L., *Lancet*, 1932, 2, p. 1202.

(14) Moynihan, B. J. A., *Lancet*, 1911, 2, p. 430.

(15) Delore, P., *Lyon méd.*, 1928, 141, p. 601.

(16) Hartman, H. R., *Am. J. Med. Sc.*, 1921, 162, p. 201.

(17) Hochrein, M., *München. med. Wchnschr.*, 1924, 76, p. 1327.

(18) Morawitz, P., *Arch. f. Verdauungskr.*, 1930, 47, p. 305.

(19) Campbell, J. M. H., and Conybeare, J. J., *Guy's Hospital Rep.*, 1922, 72, p. 265.

(20) Dennig, H., *München. med. Wchnschr.*, 1929, 76, p. 633.

(21) Glanvill, R., and Hurst, A. F., *Guy's Hospital Rep.*, 1930, 80, p. 411.

(22) Faber, K., *Berl. klin. Wchnschr.*, 1913, 50, p. 958.

(23) Witts, L. J., *Guy's Hospital Rep.*, 1930, 80, p. 253.

(24) Lublin, H., *Acta med. Scandinav.*, 1931, Suppl. xli.

(25) Hurst, A. F., and Cosin, C. F., *Guy's Hospital Rep.*, 1930, 80, p. 414.

(26) Davies, D. T., *Quart. J. Med.*, 1931, 24, p. 447.

(27) Meulengracht, E., *Acta med. Scandinav.*, 1929, 72, p. 231.

(28) Vaughan, J. M., *Lancet*, 1932, 2, p. 1265.

(29) Bolton, C., *Brit. Med. Jour.*, 1923, 2, p. 269.

(30) Deganello, V., *Arch. ital. de biol.*, 1900, 33, p. 118.